UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,358	01/07/2002	Toshiaki Tagawa	P21620	9232

7055 7590 11/15/2005

GREENBLUM & BERNSTEIN, P.L.C.
1950 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,358	TAGAWA ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-12,15-24 and 26-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12 and 15-24 and 26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 8-8-05 is acknowledged.

Claims included in the prosecution are 10-12 and 15-24 and 26-37.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 10-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Tagawa (5,264,221).

Tagawa discloses liposomal compositions wherein the liposomes have maleimide residues on the surface. A protein (monoclonal antibody) and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues. The liposomes encapsulate the anti-cancer drug, Adriamycin (note the abstract, col. 2, line 45 through col. 5, line 27 and examples). The mol. percent of the bonded compound as disclosed in the reference on col. 4, lines 59-68 appear to fall within the claimed range. The degree of polymerization of PEG is 20-400 as noted from col. 4, line 20 which corresponds to instant molecular weights.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant admits that 221 teaches 0.1 mole % to 20 mole % antibody

(which equates to 0. 3 to 60 mg) and in examples 2 and 3 uses 5 mg of antibody /100 mg lipid. However, according to applicant since the since instant range which is within the range of the prior art gave unexpected results, the reference is not anticipated. These arguments are not found to be persuasive. According to applicant's own admission on page 17, lines 4-10, "A review of Fig. 3 in applicant's application, when comparison is made to the DXR-administered group, reveals significant inhibitory effects against tumor proliferation in the samples with the amounts of bonded antibodies within the range of 0.5 to 5.3 mg/100 mg of total lipids". This statement clearly indicates that irrespective of whether the antibody amount is outside the claimed range or inside the claimed range the results are significant meaning that even 221 results are unexpected. Therefore, the reference is still a 102 reference. Furthermore, the experiments were done with liposomes, which also have bonded PEG whereas claim 10 does not recite the requirement for PEG.

Applicant himself admits on page 14, second paragraph of the response, Tagawa teaches 0.1 to 20 mole percent and this amount falls within the range claimed in claim 10. According to applicant, the amounts now expressed in mg, correspond to the original mole percentages. Furthermore, as pointed out in the previous action, according to applicant's own statement on page 15 of the previous response, only half of the maleimidated lipid is assumed to be present outside the liposome and therefore, the percentages taught by Tagawa on col. 4, correspond to both antibody and the compound loaded with PEG compound.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 10-12 and 15-24 and 26-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagawa cited above.

As pointed out above, Tagawa discloses liposomal compositions wherein the liposomes have maleimide residues on the surface. A protein (monoclonal antibody) and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues. The liposomes encapsulate the anti-cancer drug, Adriamycin (note the abstract, col. 2, line 45 through col. 5, line 27 and examples). Tagawa's does not teach the entire claimed range of the bonded compound and the bonded antibody. However, on col. 4, line 53 et seq., Tagawa teaches the activation of the liposome first, that is introducing excess amount of maleimide groups and then reacting first with the thiol activated antibody and then blocking the remaining maleimide groups on the liposomes with excess amount of thiol modified PEG. Furthermore, in Example 2 on col. 7, Tagawa uses 5 mg of Fb' per hundred mg of lipid and this amount is instantly claimed 5 mg per 100 mg lipid. From these teachings, it is deemed obvious to one of ordinary skill in the art to manipulate the

amounts of the thiol activated antibody, since this amount depends upon the amount of the corresponding receptors on/in the host cell and then block the rest of the maleimide groups on the liposomes with the thiol modified PEG. Instant invention therefore, is deemed to be an obvious extension of prior art's teachings.

Applicant's arguments have been fully considered, but are not found to be persuasive. Although applicant does not provide specific arguments separately for the 103 rejection over 221 (Tagawa), applicant appears to argue on page 23 last paragraph that the amounts of PEG in 221 are different from instant amounts. These arguments are not persuasive. A careful review of instant Fig. 2 which shows the concentration of DXR in plasma plateaus at 15 mole percent and therefore, one would expect the same values for DXR even beyond 30 mole percent, that is at the PEG mole percentages in the prior art. Applicant has not shown any unexpected results and therefore, the rejection is maintained.

3. Claims 10-12 and 15-24 and 26-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin et al (Biochemistry, 1997) of record in combination with Tagawa cited above.

Kirpotin et al disclose sterically stabilized liposome compositions wherein the antibody is conjugated to maleimide terminated membrane anchor lipid. The polymer used is PEG. Kirpotin however, does not indicate the amounts of the antibody conjugated to the lipid in terms of mg per 100 mg lipid, but instead in mg/ml antibody to 7-10 mM liposomes (note the abstract and Material and methods and Discussion sections). Assuming that the amounts are different, in the absence of showing

unexpected results, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of targeting antibody to obtain the best possible results that is, reaching the target cancer cells expressing the corresponding antigen on the cell surface. One of ordinary skill in the art would be motivated further to vary the amounts since the reference of Tagawa as discussed above, shows that one can bind various amounts of antibody to the bilayer forming lipid. Kirpotin does not teach antibodies other than anti-HER2; however, it is deemed obvious to one of ordinary skill in the art to use any antibody including claimed GAH antibody, which Tagawa (221) uses, since the principle of targeting to the cancer cells is the same. Kirpotin does not teach the treatment of stomach or colon cancer. However, since the liposomes are only delivery devices, it is deemed obvious to one of ordinary skill in the art to choose a specific cancer drug, which is effective against a selected cancer using the liposomes taught by Kirpotin.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed the arguments regarding Tagawa. Applicant's only argument regarding Kirpotin is that it does not overcome the deficiencies of Tagawa. This argument is not found to be persuasive since Kirpotin essentially teaches antibody and PEG bound liposomes and the treatment of cancer just as in instant invention. As pointed out above, applicant has not shown any unexpected results by varying the amounts of the antibody and PEG in prior art's teachings.

Upon consideration, the 103 rejections over Tagawa 948 and 101 are withdrawn.

4. Claims 10-12, 26-31, 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagawa (5,556,948) or Tagawa (5,686,101).

Tagawa in 948 and 101discloses liposomal compositions wherein the liposomes have maleimide residues on the surface. A protein (growth factors, monoclonal antibodies and polyclonal) and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues. The liposomes encapsulate the anti-cancer drug, Adriamycin and or other drugs (note the abstract, col. 2, line 45 through col. 6, line 12 and examples in both patents). Since the examples indicate the amounts of the components in terms of mg, it is unclear whether they correspond to the claimed molar amounts. Assuming that they are different, it is deemed obvious to one of ordinary skill in the art to vary the amounts to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that in 948 0r 101, the antibody is bound to PEG whereas in instant invention, the antibody and PEG are separately bound to the liposomal surface. Based on these structural differences, the claims, which recite both antibody and PEG, are removed from this rejection. The prior art still reads on the claims which recite only antibodies since instant claims do not exclude the bonding of the antibodies to malemiide groups present on PEG which is linked to the liposomal surface. Instant claim 10 recites, "an antibody is bonded through a thioether group to a liposome comprising lipids whose' partial component as maleimidated terminal.

4. Claims 10-12 and 15-24 and 26-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hosokawa (6,787,153) or Hosokawa (6,139,869).

Hosokawa in 153 and 869 discloses liposomal compositions wherein the liposomes have maleimide residues on the surface. A protein (monoclonal antibody, GAH and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues. The liposomes encapsulate the anti-cancer drug, Adriamycin and or other drugs (note the abstract, col. 4, line 47, col. 5, line 39, Examples, examples 7 and 8 specifically and claims in both patents). Since the examples indicate the amounts of the components in terms of mg, it is unclear whether they correspond to the claimed molar amounts. Assuming that they are different, it is deemed obvious to one of ordinary skill in the art to vary the amounts to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant admits on page 26 of the response that the HosoKawa 153 and 869 disclose the same amount of antibody and the same amount of PEG as Tagawa 221 and therefore, the examiner's response is similar to that for their arguments regarding Tagawa, 221.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Upon consideration, the double patenting rejections over Tagawa 948 and 101 are withdrawn.

7. Claims 10-12, 15-23 and 26-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,787,153. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in both patented case and instant application are drawn to liposome compositions wherein both an antibody and PEG are attached to the liposome surface through maleimidated terminals of the lipid moiety. Instant claims are generic with respect to the antibody and a genus anticipates the species of antibody claimed in the patented claims. The patented claims are generic with respect to the amounts of the antibody per 100 mg of lipid claimed in instant claims. Amounts are deemed to be obvious manipulatable parameters practiced by an artisan.

8. Claims 10-12, 15-23 and 26-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,139,869. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in both patented case and instant application are drawn to liposome compositions wherein both an antibody and PEG are attached to the liposome surface through maleimidated terminals of the lipid moiety. Instant claims are generic with respect to the antibody and a genus anticipates

the species of antibody claimed in the patented claims. The patented claims are generic with respect to the amounts of the antibody per 100 mg of lipid claimed in instant claims. Amounts are deemed to be obvious manipulatable parameters practiced by an artisan.

These rejections are maintained since applicant provides no specific arguments with regard to the rejections.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK